UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,836	03/30/2006	Angelo Guglielmotti	281760US0PCT	6824

22850 7590 09/12/2007

OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER
RAMACHANDRAN, UMAMAHESWARI

ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
09/12/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@oblon.com
oblonpat@oblon.com
jgardner@oblon.com

Office Action Summary	Application No.	Applicant(s)	
	10/560,836	GUGLIELMOTTI ET AL.	
	Examiner	Art Unit	
	Umamaheswari Ramachandran	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner notes the receipt of the amendments and remarks received in the office on 6/19/2007 canceling claims 1-5 and adding new claims 6-23. Claims 6-23 are pending and are being examined on the merits herein.

Response to Remarks

The rejection of claim 5 under 35 U.S.C 112(2) is withdrawn due to the cancellation of claim 5. The rejection of claims 1-4 under 35 U.S.C. 103(a) as being unpatentable over Gaster et al (EP 0630736) in view of Smith et al. (Neuroscience Letters, 271, 1999, 61-64) and further in view of Jorum et al. (Pain, 101, 2003, 229-235) is withdrawn due to the cancellation of claims 1-4. The rejection of claims 1-4 under 35 U.S.C. 103(a) as being unpatentable over Gaster et al (EP 0630736) in view of Burstein et al. (Brain, 2000, 123, 1703-1709) and further in view of Jorum et al. (Pain, 101, 2003, 229-235) is withdrawn due to the cancellation of claims 1-4. Applicants' addition of new claims necessitated the modified and new grounds of rejection presented in this office action. Hence the Office Action is made Final.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6, 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter,

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 1 and claim 13 has a limitation 'cyclohexylmethyl group'. The specification of the instant application teaches compound of formula I wherein R is cyclohexyl, prepared according to the examples 23 of EP A-0-630-376 (p 6, lines 11-13, p 7, lines 12-14). The specification teaches clearly that R is cyclohexyl in compound of formula I and is prepared according to example 23 and implies that compound of formula I with R being cyclohexyl is prepared following the method according to example 23 of EP A-0-630-376. It does not teach or imply that R is cyclohexylmethyl. Hence this limitation is a new matter and does not have support in the specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6-12, 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gaster et al (EP 0630736) in view of Smith et al. (Neuroscience Letters, 271, 1999, 61-64) and further in view of Jorum et al. (Pain, 101, 2003, 229-235).

Gaster et al. teaches the compounds of formula I (claim 1) to be 5-HT4 antagonists (p1 lines 6-8) and further teaches a method of treatment of irritable bowel syndrome, migraine etc in mammals (p6, lines 42-43) comprising administering these

compounds. The reference does not teach a method of treatment of neuropathic pain comprising administering such compounds.

Smith et al. teaches that 5-HT4 receptor antagonist such as SB 207266 potentiates inhibition of intestinal allodynia (see Abstract, p63, lines 11-12).

The reference does not teach allodynia to be neuropathic pain.

Jorum et al. teaches that allodynia and hyperalgesia are frequent clinical findings in patients with neuropathic pain (p 229, lines 1-5).

It would have been obvious to one skilled in the art to use the compounds of formula I in the treatment of neuropathic pain. The motivation to do is provided by Gaster, Smith et al. and Jorum et al. Gaster et al. teaches the compounds of formula I (claim 1) to be 5-HT4 antagonists. Smith et al. teaches that 5-HT4 receptor antagonist such as SB 207266 shows an anti-allodynic activity and Jorum et al. teaches that allodynia and hyperalgesia are frequent clinical findings in patients with neuropathic pain. Hence inhibiting allodynia in patients provides a method of treatment of neuropathic pain. One of ordinary skill in the art would have been motivated to use one 5-HT4 receptor antagonist (compound of formula I) for another 5-HT4 receptor antagonist (SB 207266) in the treatment of allodynia (clinical finding of neuropathic pain) in expectation of success as Smith teaches an anti-allodynic effect of an 5-HT4 receptor antagonist.

Claims 6-12, 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gaster et al (EP 0630736) in view of Burstein et al. (Brain, 2000, 123, 1703-1709) and further in view of Jorum et al. (Pain, 101, 2003, 229-235).

Gaster et al's teachings as above.

The reference does not teach a method of treatment of neuropathic pain comprising administering such compounds.

Burstein et al. teaches that most migraine patients exhibit cutaneous allodynia during a fully developed migraine attack (See Abstract).

The reference does not teach allodynia to be neuropathic pain.

Jorum et al. teaches that allodynia and hyperalgesia are frequent clinical findings in patients with neuropathic pain (p 229, lines 1-5).

It would have been obvious to one skilled in the art to use the compounds of formula I in the treatment of neuropathic pain. The motivation to do is provided by Gaster et al, Burstein et al. and Jorum et al. Gaster et al teaches the administration of a 5-HT4 antagonist is of potential benefit in relieving migraine attack. Burstein et al. teaches that cutaneous allodynia is exhibited during a fully developed migraine attack and Jorum et al. teaches that allodynia and hyperalgesia are frequent clinical findings in patients with neuropathic pain. Hence by treating migraine attacks in patients allodynia is treated and in turn the neuropathic pain.

Claims 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gaster et al (EP 0630736) in view of Smith et al. (Neuroscience Letters, 271, 1999, 61-64) and further in view of Jorum et al. (Pain, 101, 2003, 229-235) as applied to claims 6-12, 14-17 and further in view of Wickenden et al. (U.S. 6,326,385).

Gaster et al., Smith et al. and Jorum et al's teachings discussed as above.

The references do not teach the subject has neuropathic pain associated with disorders such as diabetes, cancer, trigeminal neuralgia etc.

Wickenden et al. teach that neuropathic pain is associated with injury to the central or peripheral nervous system due to cancer, diabetes, diabetic neuropathy, trigeminal neuralgia (col. 27, claim 8).

It would have been obvious to one skilled in the art to use the compounds of formula I in the treatment of neuropathic pain associated with diabetes, cancer or trigeminal neuralgia. The motivation to do is provided by Gaster, Smith et al. and Jorum et al. Gaster teach the compounds of formula I as 5-HT4 receptor antagonists. Smith et al. teaches that 5-HT4 receptor antagonist such as SB 207266 shows an anti-allodynic activity and Jorum et al. teaches that allodynia and hyperalgesia are frequent clinical findings in patients with neuropathic pain. One of ordinary skill in the art would have been motivated to use one 5-HT4 receptor antagonist (compound of formula I) for another 5-HT4 receptor antagonist (SB 207266) in the treatment of allodynia (clinical finding of neuropathic pain) in expectation of success as Smith teaches an anti-allodynic effect of an 5-HT4 receptor antagonist. One of ordinary skill in the art would have been motivated by expectation of success in using compounds of formula I of the instant application in the treatment of neuropathic pain associated with disorders such as diabetes, cancer or trigeminal neuralgia.

Claims 20-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gaster et al (EP 0630736) in view of Smith et al. (Neuroscience Letters, 271, 1999, 61-64) and further in view of Jorum et al. (Pain, 101, 2003, 229-235) as applied to claims 6-

12, 14-17and further in view of Omoigui (US 2004/0038874, effective filing date Aug 22 2002).

Gaster et al., Smith et al. and Jorum et al's teachings discussed as above.

The references do not teach the subject has neuropathic pain associated with disorders such as trigeminal neuralgia, trauma, post-herpetic syndrome etc. and the route of administration of compound of formula I.

Omoigui teach a method of treating persistent pain disorders including neuropathic pain by inhibiting the biochemical mediators of inflammation in a subject comprising administering to said subject a therapeutically effective dosage of said inhibitor such as serotonin receptor antagonist (see Abstract, p 11, claim 1, p 13, claim 80). The reference further teaches the underlying basis for pain including neuropathic is inflammation and antagonism of inflammatory response will relieve pain of every type, origin and character (p 1, para 004). The reference teaches that hallmarks of neuropathic pain are chronic allodynia and hyperalgesia (para 0072). The reference teaches persistent pain disorder is neuropathic pain syndrome including neuralgia, post herpetic neuralgia (p 11, claim 12, 36). The reference further teaches that serotonin receptor antagonist is administered intramuscularly, intravenously, subcutaneously, orally or rectally.

It would have been obvious to one skilled in the art to use the compounds of formula I in the treatment of neuropathic pain associated with neuralgia, trigeminal neuralgia or post herpetic syndrome. The motivation to do is provided by Gaster, Smith et al and Omoigui. Gaster teach the compounds of formula I as 5-HT4 receptor

antagonists. Smith et al. teaches that 5-HT4 receptor antagonist such as SB 207266 shows an anti-allodynic activity. Omaigui teach a method of administering to said subject a therapeutically effective dosage of inhibitor such as serotonin receptor antagonist for the treatment of neuropathic pain such as trigeminal neuralgia, post herpetic syndrome etc. In addition, Omoigui further teach hallmarks of neuropathic pain are chronic allodynia and hyperalgesia. One of ordinary skill in the art would have been motivated to use one 5-HT4 receptor antagonist (compound of formula I) for another 5-HT4 receptor antagonist (SB 207266) in the treatment of allodynia (clinical finding of neuropathic pain) in expectation of success as Smith teaches an anti-allodynic effect of an 5-HT4 receptor antagonist. One of ordinary skill in the art would have been motivated by expectation of success in using 5-HT4 receptor antagonist in a method of treatment of neuralgia or post herpetic syndrome as Omoigui teaches serotonin receptor antagonists are effective in the treatment of neuropathic pain with such syndromes.

Response to Arguments

Applicants' argue that premises of treating allodynia would also ameliorate neuropathic pain is incorrect. In response, Jorum et al. teaches that allodynia and hyperalgesia are frequent clinical findings in patients with neuropathic pain. In addition other prior art such as Omoigui teaches that hallmarks of neuropathic pain are chronic allodynia and hyperalgesia. Hence it would have been obvious to one of ordinary skill in the art at the time of the invention to administer a 5-HT4 receptor antagonist compound in the treatment of neuropathic pain where another 5-HT4 receptor antagonist

compound has been shown to be effective in the treatment of allodynia, a clinical finding of neuropathic pain.

Applicants' argue that office has not explained why a compound of formula I would exhibit similar properties to the structurally distinct SB-207266 compound of Smith. In response, Gaster et al. teaches the compounds of formula I (claim 1) to be 5-HT4 antagonists and Smith teach SB-207266 to be 5-HT4 antagonist. One of ordinary skill in the art would have been motivated to use one 5-HT4 receptor antagonist (compound of formula I) for another 5-HT4 receptor antagonist (SB 207266) in the treatment of allodynia (clinical finding of neuropathic pain) in expectation of success as Smith teaches an anti-allodynic effect of an 5-HT4 receptor antagonist.

Applicants' argue that Jorum disclose Alfentanil significantly reduced cold allodynia and it is a non-analogous art because it discloses a different class of drugs and does not disclose compounds of formula I (p 7, para 3, remarks/arguments). In response, Jorum et al. has been used as a secondary reference to show allodynia and hyperalgesia are frequent clinical findings in patients with neuropathic pain and in no way as a reference to the drug Alfentanil.

Applicants' argue that Burstein teaches or suggests that any class of drugs capable of treating cutaneous allodynia will successfully treat migraine or neuropathic pain. In response, the applicants are right that it does not teach or suggest any class of drugs for the treatment of neuropathic pain but the secondary reference has been used to show the development of cutaneous allodynia during a migraine attack in most migraine patients. Gaster et al teaches the administration of a 5-HT4 antagonist is of

potential benefit in relieving migraine attack. Hence it would have been obvious to one of ordinary skill in the art at the time of the invention that cutaneous allodynia is treated when migraine is treated. Hence by treating migraine attacks in patients, allodynia (a clinical symptom of neuropathic pain) is treated and in turn the neuropathic pain.

Conclusion

No Claims are allowed.

Applicants' cancellation and addition of new claims necessitated the modified and new rejections presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

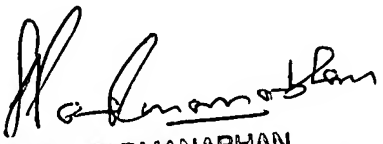
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Umamaheswari Ramachandran whose telephone number is 571-272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

***



SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER